Elevated Creatine and Myo-Inositol Levels Correlate with Verbal and Visual Memory Tasks in Mild Cognitive Impairment

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Introduction: ^{1}H-MRS is a widely-used non-invasive tool for neurochemical profiling that has been recently applied to the study of mild cognitive impairment (MCI), (1,2). MCI patients have abnormal memory functioning for age but do not have the extensive cognitive deficiencies seen in individuals with Alzheimer's disease (AD). They are an important group for study as they are at increased risk for development of AD (3). Previous studies have suggested that the most important ^{1}H-MRS biomarkers of MCI are: N-acetyl-aspartate (NAA), a marker of neuronal integrity; and myo-Inositol (mI), a cerebral osmolyte considered to be an intracellular messenger and a marker of gliosis. The neurochemical profile of MCI is often characterized by decreased NAA/tCr and increased mI/tCr relative to healthy controls, where tCr (creatine + phosphocreatine) is a marker of energy metabolism. However, this neurochemical profile of MCI is derived from intermediate and long echo time studies, 20-45 ms and 135-270 ms, respectively, under the assumptions that tCr is a stable metabolite and that T_2-weighting is negligible. In this work, we examine the validity of these assumptions through the utility of short echo time (10 ms) spectroscopy to directly negate the effects of T_2-weighting and an absolute quantitation technique to remove the concentration dependency on tCr.

Method: Participants were 9 patients fulfilling the Petersen criteria for MCI (3) and 8 healthy elderly (HE) adults. All participants completed a battery of neuropsychological tests including a rote verbal list-learning task – the California Verbal Learning Test-II (CVLT-II) (4) – and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (5) which contains a measure of visual memory (picture recall). Each participant also underwent a spectroscopy examination that included a STEAM experiment (VOI~6cm^3, TE/TM/TR = 10/10/5000 ms, 112 excitations, 2500Hz spectral width, and 819.2 acquisition window), a water reference experiment for phase correction, and a progressive TR T_2 experiment (6) for compartmental analysis and absolute quantitation. All ^{1}H MRS data were collected along the midline of the posterior cingulate gyrus using a 1.5 T Siemens Magnetom Sonata MRI system. QUEST was used to identify the metabolite resonances and the macromolecule background (7). Concentrations are reported in millimoles per kilogram of tissue water (8).

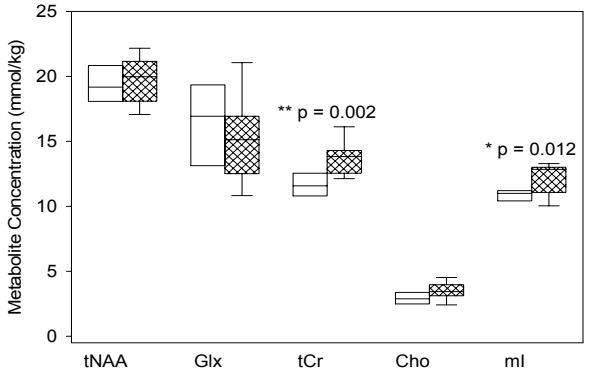

Figure 1. HE ☐ and MCI ▨ metabolite concentrations are shown for tNAA (total N-acetyl-aspartate), Glx (glutamate+ glutaminte), tCr (creatine+phosphocreatine), Cho (choline containing compounds), and mI (myo-Inositol). tCr and mI were significantly higher in MCI versus HE participants.

Results and Discussion: We found significantly elevated levels of tCr ($p = 0.002$) and mI ($p = 0.012$) in the MCI subjects relative to controls (Fig 1). If metabolite ratios are calculated relative to tCr, then our data shows a trend consistent with Kantarci et al -decreased NAA/tCr, increased Cho/tCr, and increased mI/tCr (1) in the MCI group. Post hoc comparisons between the psychometric measures and the tCr and mI concentrations revealed significant negative correlations ($p < 0.01$) with indices of visual (RBANS_pr) and verbal (CVLT_ldf) recall (Table 1). That is, increased metabolite concentrations were associated with reduced performance on memory measures. There was no significant correlation with a general measure of cognitive integrity (Stroop color-word), indicating that the changes in tCr and mI may be specific to the site (posterior cingulate) and/or to the cognitive process (memory). Multiple linear regression of mI and tCr on the scores for visual and verbal memory yielded correlation coefficients of 0.797 and 0.814, respectively, with a minimum power of 98% for each regression. These results are consistent with the hypothesis (9) that creatine may act as a neuroprotective agent during the pre-clinical stages of AD. If MCI truly represents the prodomal stage of AD, characterized by subtle increases in cerebral atrophy and hypoglucose metabolism, then long-term elevations in resting creatine levels may partially offset the energy deficits from impaired aerobic glycolysis. Thus, increased creatine levels could be a natural adaptive response, indicative of disease severity in MCI. Therefore, the use of ratios relative to creatine may obscure a potentially powerful marker of MCI.

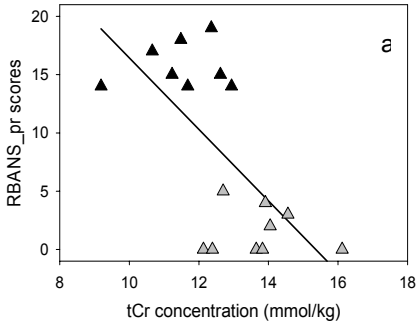

Table 1.Correlation Analyses

Test	Metabolite	r	p
RBANS_pr	tCr	-0.661	0.004
CVLT_ldf	tCr	-0.680	0.003
RBANS_pr	mI	-0.586	0.014
CVLT_ldf	mI	-0.592	0.012

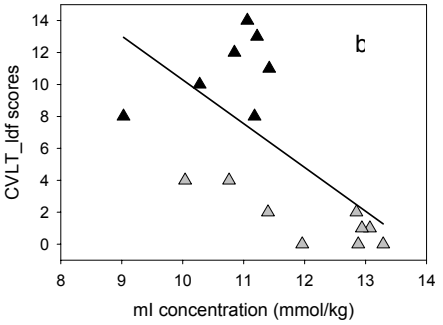

Figure 2. Psychometric measures and metabolite concentrations for HE (▲) and MCI (▲). **Table 1** summarizes the significant correlations between metabolites and measures of cognitive function as assessed by RBANS_pr for visual memory and CVLT_ldf for verbal memory. Examples of regressions are shown in (a) and (b), and Table 1 shows that all linear regressions have strong negative correlations. Multiple linear regressions of tCr and mI on memory tasks improved the correlation coefficients to 0.797 for RBANS_pr and 0.814 for CVLT_ldf.

References:(1) Kantarci K et al. *AJNR* 2003;24:843-9.(2) Modrego PJ et al. *Am J Psychiatry* 2005;162:66775. (3) Petersen RC et al. *Arch Neurol* 1999;56:303-8. (4) Delis, D et al. (2000) The Psychological Corporation. (5) Randolph, C (1998) The Psychological Corporation. (6) Knight-Scott J et al. *J Magn Reson* 2005;173:169-74.(7) Ratiney H et al. *MAGMA* 2004;16:28496.(8) Knight-Scott J et al. *Magn Reson Imag* 2003;21:787-97.(9) Balestrino M et al. *Amino Acids* 2002;23:221-9.